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(54) Title: FORMULATIONS FOR DELIVERY OF OSTEOGENIC PROTEINS

(57) Abstract

A composition is disclosed comprising a pharmaceutically acceptable admixture of an osteogenic protein; a porous particulate polymer matrix; an osteogenic protein-sequestering amount of blood clot; and a calcium sulfate hemihydrate-containing substance. Also disclosed are formulations of bone morphogenetic proteins with improved solubility and/or stability characteristics.

What is claimed is:

1. A composition comprising a pharmaceutically acceptable admixture of

(i) an osteogenic protein;

(ii) a porous particulate polymer matrix;

(iii) an osteogenic protein-sequestering amount of autogenous blood; and

(iv) a calcium sulfate hemihydrate-containing substance.

2. The composition of claim 1 wherein the osteogenic protein is selected from the group consisting of the members of the BMP-family.

3. The composition of claim 2 wherein the osteogenic protein is BMP-2.

4. The composition of claim 1 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.

5. The composition of claim 1 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.

6. The composition of claim 1 wherein the admixture is free from antifibrinolytic agents.

7. The composition of claim 2 wherein the admixture is free from antifibrinolytic agents.

8. The composition of claim 3 wherein the admixture is free from antifibrinolytic agents.

9. A composition comprising a pharmaceutically acceptable admixture of

(i) BMP-2;

(ii) a polymeric matrix component comprising porous particles having a diameter of between about 150 and 850 microns and a porosity such that the surface area of the particles is between about 0.01 and 4.0 m^2/g;

(iii) a protein sequestering amount of autogenous blood;

and

(iv) a calcium sulfate hemihydrate-containing substance.

10. The composition of claim 9, wherein the polymer is selected from the group consisting of poly(lactic acid), poly(glycolic acid), and copolymers of lactic acid and glycolic acid.

11. The composition of claim 9 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.

12. The composition of claim 9 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.

13. A kit for the repair of cartilage and/or bone injuries which comprises:

(i) an osteogenic protein;

(ii) a porous particulate polymer matrix; and

(iii) a calcium sulfate hemihydrate-containing substance.

14. The kit of claim 13 wherein the calcium sulfate hemihydrate-containing substance is Plaster of Paris.

15. The composition of claim 13 wherein the calcium sulfate hemihydrate-containing substance is a mixture of Plaster of Paris and hydroxyapatite.

16. A composition comprising a pharmaceutically acceptable admixture of

(i) an osteogenic protein;

(ii) a porous particulate polymer matrix;

(iii) a protein-sequestering agent; and

(iv) an antibiotic substance selected from the group consisting of vancomycin and gentamycin.

17. The composition of claim 16, wherein the protein-sequestering agent is selected from the group consisting of cellulosic materials, hyaluronic acid, alginates, autogenous blood, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer, and poly(vinyl alcohol).

18. The composition of claim 17, wherein the protein sequestering agent is a cellulosic material selected from the group

consisting of alkylcelluloses (including hydroxy-alkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose.

19. The composition of claim 18, wherein the cellulosic material is diluted with aqueous glycerol.

20. A composition comprising a pharmaceutically acceptable admixture of

(i) an osteogenic protein;

(ii) a calcium sulfate hemihydrate-containing substance; wherein said admixture is diluted in aqueous solution, the components of said admixture being present in relative amounts of about 1 gram of osteogenic protein; about 12 grams of calcium sulfate hemihydrate-containing substance; and about 3 ml water.

21. A composition comprising an osteogenic protein, about 0.1 to about 5.0% (w/v) of a sugar, about 1.0 to about 10.0% (w/v) glycine, and about 1 to about 20 mM of glutamic acid hydrochloride, wherein such formulation has a pH of about 4.5.

22. The formulation of claim 21, further comprising about 0.01 to about 0.1 % (w/v) of a non-ionic surfactant.

23. A composition comprising an osteogenic protein, about 1 to about 10% (w/v) glycine, about 0.1 to about 5.0% (w/v) sucrose about 0.01 to about 0.1% (w/v) non-ionic surfactant and about 5 to about 10 mM glutamic acid hydrochloride, wherein such formulation has a pH less than about 6.0.

24. A composition comprising an osteogenic protein, about 2.5% (w/v) glycine, about 0.5% (w/v) sucrose, about 5 mM glutamic acid hydrochloride, and about 0.01% (w/v) polysorbate 80, wherein such formulation has a pH of about 4.5.

25. A composition comprising a lyophilized formulation of about 3.12% to about 24.38% (w/w) BMP; about 0.52% to about 10.27% (w/w) glutamic acid hydrochloride; about 38.4% to about 75.7% (w/w) glycine; about 14.28% to about 47.15% (w/w) sucrose; and optionally about 0.15% to about 2.94% (w/w) polysorbate 80.

26. A composition according to claim 25 wherein the

formulation comprises relative weight amounts of about 4.0 mg/ml of BMP-2; about 0.918 mg/ml of glutamic acid hydrochloride; about 25 mg/ml of glycine; about 5 mg/ml of sucrose; and optionally about 0.1 mg/ml of polysorbate 80.

27. A composition according to claim 25 wherein the formulation comprises relative weight amounts of about 2.0 mg/ml of BMP-2; about 0.918 mg/ml of glutamic acid hydrochloride; about 25 mg/ml of glycine; about 5 mg/ml of sucrose; and optionally about 0.1 mg/ml of polysorbate 80.